IN THE UNITED STATES PATENT AND TRADE MARK OFFICE

In re application of

Mitsutaka Nakamura et al.

Application No.: 10/525,021 Art Unit: 1617

Filed: February 18, 2005 Examiner: F. Krass

For: Agent for Treatment of Schizophrenia

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. § 1.132

Declaration Under 37 C.F.R. 1.132

Sir:

I, Masaaki Ogasa, citizen of Japan and residing at One Bridge Plaza, Suite 510, Fort Lee, New Jersey, 07024 USA, declare and say as follows.

1. I am a graduate of Faculty of Pharmacy, Kyoto Pharmaceutical University, Japan in 1991 and of Master Course, same university in 1993.

2. Since 1993 up till the present, I have been an employee of Dainippon Sumitomo Pharma Company, Limited. (Former Sumitomo Pharmaceuticals, Company, Limited), the assignee of U.S. Patent Application No. 10/525,021 and I have been engaged in research and development of lurasidone for the treatment of psychiatric disease at the Research Center and Clinical Development Department of said company.

3. Under my direction, the following comparative clinical studies have been done.

A STUDY OF THE MAXIMUM TOLERATED DOSE OF SM-13496 (LURASIDONE) IN PATIENTS WITH SCHIZOPHRENIA (Study D1050217)

Study Design and Methodology

This was a single-center, randomized, in-patient, double-blind study to determine the safety and tolerability of lurasidone administered as repeated oral doses to stable schizophrenic patients. In order to determine the maximum tolerated dose (MTD) of lurasidone, study drug was administered to 7 fixed dose, sequential, escalating dose cohorts (cohorts 1–7) that were planned to consist of a minimum of 6 and maximum of 10 patients each (2 placebo and up to 8 lurasidone patients). The minimum intolerable dose (MID) was defined as the dose at which a minimum of 4 evaluable lurasidone-treated patients in a cohort experienced more than 1 occurrence of moderate or severe adverse events related to the lurasidone, or the dose at which at least 1 lurasidone-treated patient experienced a serious adverse event at least possibly related to lurasidone. The next dose level below the MID was designated the MTD.

Following a screening period of up to 30 days, eligible patients entered a 4 day in patient single-blind placebo washout period during which they discontinued any previous antipsychotic and any other prohibited psychotropic medications. At the end of the washout period, patients were randomized to receive lurasidone or placebo once daily. Patients were enrolled into the first 7 cohorts and received study drug on Days 1–6, and the lurasidone doses per cohort were: 160 mg (cohort 1), 200 mg (cohort 2), 240 mg (cohort 3), 280 mg (cohort 4), 320 mg (cohort 5), 400 mg (cohort 6) and 520 mg (cohort 7). The MID was reached in cohort 7. All study drug doses were administered to patients in a postprandial state at approximately 8:00 AM.

Results: Determination of the Minimum Intolerable Dose (MID)

The MID was defined as the dose at which a minimum of 4 evaluable lurasidone treated patients in a cohort each experienced more than 1 occurrence of moderate or severe adverse experiences related [relationship of possibly, probably, or definitely] to the lurasidone, or the dose at which at least 1 lurasidone treated patient experienced a serious adverse experience at least possibly related to lurasidone). The number of patients experiencing more than 1 moderate or severe lurasidone-related adverse experience by lurasidone dose was 0 (160 mg), 1 (200 mg), 1 (240 mg), 1 (280 mg), 0 (320 mg), 2 (400 mg), and 5 (520 mg) (Table 1). There were no serious adverse experiences at least possibly related to lurasidone. Therefore, the MID was lurasidone 520 mg. Among patients who received the MID in the fixed-dose cohorts (lurasidone 520 mg), the moderate and severe adverse experiences were akathisia (5 patients); sedation (3 patients); restlessness (2 patients); anxiety (1 patient, event was severe); and extrapyramidal

disorder, muscle spasm, depressed level of consciousness, claustrophobia, bruxism, and dystonia (1 patient each).

Table 1 Patients Reaching MID Criteria by Lurasidone Dose

		Patients with More than 1 Moderate or Severe Treatment-Related Adverse Events	
Lurasidone Dose		Adverse Eventa	
160 mg	(N=6)	none	--
200 mg	(N=5)	01-203	nausea, vomiting NOS
240 mg	(N=7)	01-303	dystonia, vomiting NOS
280 mg	(N=6)	01-406	bruxism, trismus
320 mg	(N=7)	none	--
400 mg	(N=6)	01-601	sedation, restlessness
		01-605	akathisia, vomiting NOS, nausea
520 mg	(N=7)	01-702	akathisia, extrapyramidal disorder, muscle spasm
		01-703	akathisia, sedation, depressed level of consciousness
		01-704	akathisia, restlessness
		01-705	akathisia, anxiety (severe), restlessness, claustrophobia
		01-708	akathisia, bruxism, dystonia

NOS = not otherwise specified

a Adverse experiences were moderate in severity unless otherwise indicated

Dopamine D2 Receptor Occupancy in Healthy Male Subjects Treated with SM-13496 Using Positron Emission Tomography (PET) (Study D1050180)

Study Design and Methodology

The primary objective of this study was to determine dopamine type-2 (D2) receptor occupancy of SM-13496 at 5 single oral doses ranging from 10 mg to 80 mg in healthy male subjects. Informed consent and confirmation of eligibility were obtained for each study subject at Screening Visit 1; an MRI for brain mapping was performed at Screening Visit 2. Four subjects each were sequentially assigned to receive SM-13496 10 mg, 20 mg, 40 mg, 60 mg, or 80 mg; progression to each escalating dose cohort was based on the review of safety data. Subjects were admitted to the clinical unit on Day -1 and underwent a full physical examination, vital signs assessment, electrocardiograms, and laboratory assessments. On the following day, Day 1, baseline fasting safety labs and baseline pharmacokinetic sampling were performed, and then a baseline PET scan was performed and a standard breakfast was provided to the study subjects 30 minutes before dosing with SM-13496. A PET scan was performed at 1.5 hours after dosing.

Results:

Receptor occupancy-CPET relationships were determined in the putamen, caudate nucleus, and ventral striatum regions of the brain after oral administration of 10 mg, 20 mg, 40 mg, 60 mg, and 80 mg of SM-13496 in healthy male volunteers. An increase in percent D2 receptor occupancy was observed with each increase in SM-13496 dose up to 60 mg. Further increases in occupancy were not observed for the 80 mg group in which receptor occupancy was similar to the 60 mg group. The results for each dose group were similar among all three striatal regions. Mean D2 receptor occupancies for the 10 mg, 20 mg, 40 mg, 60 mg, and 80 mg groups for the three regions ranged from 41.3%-43.3%, 51.0%-54.8%, 63.1%-67.5%, 77.4%-84.3%, and 72.9%-78.9%, respectively.

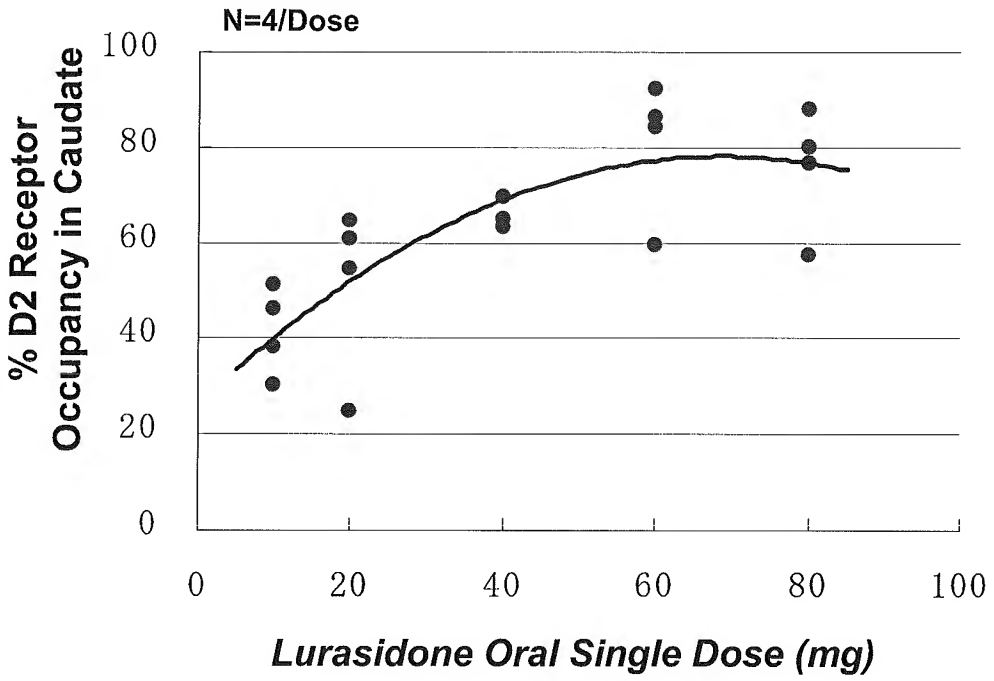

Figure 1 D_2 Occupancy by C^{11}-Raclopride in Caudate

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

This 18 day of June, 2008

M. Ogasa

Masaaki Ogasa